IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

FOREST LABORATORIES, LLC, FOREST LABORATORIES HOLDINGS, LTD., and ALLERGAN PHARMACEUTICALS INTERNATIONAL LTD., *Plaintiffs*, v. SIGMAPHARM LABORATORIES, LLC, *et al*., *Defendants*.	Civ. No. 14-1119- MSG CONSOLIDATED

MEMORANDUM OPINION

Jack B. Blumenfeld and Jeremy A. Tigan of Morris, Nichols, Arsht & Tunnell LLP, Wilmington, Del.; Howard W. Levine, Sanya Sukduang, and Jonathan R. Davies of Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, New York, NY. *Attorneys for Plaintiffs*.

Neal C. Belgam, Eve H. Ormerod, and Jennifer M. Rutter of Smith Katzenstein & Jenkins, LLP, Wilmington, Del.; Michael R. Dzwonczyk and Aiyda Cobb of Sughrue Mion, PLLC, Washington, DC. *Attorneys for Defendants Amneal Pharmaceuticals LLC, Amneal Pharmaceuticals of New York LLC, and Amneal Pharmaceuticals Co. India Pvt. Ltd.*

Stephen B. Brauerman of Bayard, P.A., Wilmington, Del.; Clifford Katz of Kelley Drye & Warren LLP, New York, NY; Douglass C. Hochstetler of Kelley Drye & Warren LLP, Chicago, Ill. *Attorneys for Defendant Breckenridge Pharmaceutical Inc.*

Karen E. Keller and Jeffrey T. Castellano of Shaw Keller LLP, Wilmington, Del.; Imron T. Aly, Joel M. Wallace, and Helen H. Ji of Schiff Hardin LLP, Chicago, IL. *Attorneys for Defendants Hikma, Pharmaceuticals LLC, Hikma, Pharmaceuticals PLC, and West-Ward Pharmaceuticals Corp*.

Karen L. Pascale and Pilar G. Kraman of Young, Conaway, Stargatt & Taylor LLP, Wilmington, Del.; Paul M. Richter, Jr. of Devlin Law Firm LLC, Wilmington, Del. *Attorneys for Defendants Alembic Pharmaceuticals Ltd, Alembic Global Holdings S/A, and Alembic Pharmaceuticals, Inc.*

Dated: July 21, 2020
Wilmington, Delaware

GOLDBERG, MITCHELL S., District Judge

Plaintiffs Forest Laboratories LLC, Forest Laboratories Holdings, Ltd., and Allergan Pharmaceuticals International Ltd. (collectively, "Forest") have sued five generic manufacturers for infringement of U.S. Patent No. 5,763,476 ("the '476 patent"): Sigmapharm Laboratories, LLC ("Sigmapharm"); Hikma Pharmaceuticals, LLC, Hikma Pharmaceuticals, PLC, and West-Ward Pharmaceutical Corp. (collectively, "Hikma"); Breckenridge Pharmaceutical, Inc. ("Breckenridge"); Alembic Pharmaceuticals Ltd., Alembic Global Holding S.A., and Alembic Pharmaceuticals, Inc. (collectively, "Alembic"); and Amneal Pharmaceuticals, LLC, Amneal Pharmaceuticals of New York, LLC, and Amneal Pharmaceuticals Co. India PVT., Ltd. (collectively, "Amneal").

The'476 patent covers the antipsychotic drug Saphris, which is approved for the treatment of schizophrenia and bipolar disorder. The '476 patent claims sublingual and buccal compositions of asenapine and their methods of use. For sublingual tablets, the patient places the formulation under the tongue and waits for it to dissolve. (D.I. 322 at 18). For buccal tablets, the formulation is placed in the pouch of the cheek. (*Id*. at 12).

After a trial in the fall of 2016 involving all of the Defendants but Sigmapharm, the Honorable Sue L. Robinson, now retired, found, among other things, that the '476 patent was not invalid for obviousness. Defendants appealed this finding to The United States Court of Appeals, Federal Circuit. *Forest Laboratories, LLC v. Sigmapharm Laboratories, LLC*, 257 F. Supp. 3d 664, 693 (D. Del. 2017). This Opinion addresses the Federal Circuit's remand directive that the Trial Court consider "the limited question of whether compliance concerns with patients who have trouble swallowing would provide a motivation to combine and its impact on the obviousness

analysis."[1] *Forest Laboratories, LLC v. Sigmapharm Laboratories, LLC*, 918 F.3d 928, 938 (Fed. Cir. 2019).

I. BACKGROUND

At trial, Defendants argued, amongst other things, that the '476 patent was invalid for obviousness because there was a motivation to develop sublingual and buccal forms of asenapine based on bioavailability concerns with the orally administered forms. *Forest*, 257 F. Supp. 3d at 687-89. In explaining why she rejected Defendants' bioavailability argument, Judge Robinson touched on compliance concerns, stating:

> If a skilled artisan did in fact want to increase asenapine's bioavailability, the most common, logical, conventional, and cost-effective means of doing this would have been to increase the dose administered to the patient. . . . This is especially persuasive reasoning given patient compliance concerns and the special instructions doctors need to provide patients when taking sublingual dosage forms. As explained by Dr. McIntyre, clinicians with experience in treating schizophrenic patients understand that sublingual dosage forms are more burdensome to schizophrenic patients in that they require the patient to hold the dosage form in the mouth under the tongue for a period of time, and also require that the patient refrain from drinking or swallowing for a period of time (ten minutes in the case of Saphris). Defendants' own expert clinician, Dr. Hollander, agreed that sublingual administration would not improve patient compliance.

Forest, 257 F. Supp. 3d at 688–89 (internal citations to the record omitted).

Defendants abandoned their bioavailability argument on appeal, asserting instead that there was a motivation to combine based on compliance concerns. *Forest*, 918 F.3d at 934. The Federal Circuit acknowledged the above passage in considering Defendants' motivation to combine argument based on compliance concerns but stated that, "[s]ummarizing testimony … is not a clear

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[1] On May 18, 2017, Chief Judge D. Brooks Smith of the United States Court of Appeals for the Third Circuit designated me as a visiting judge for the District of Delaware, pursuant to 28 U.S.C. § 292(b), to handle this and other Delaware cases.

finding." *Forest*, 918 F.3d at 934. Thus, the Federal Circuit observed that "Our review would be aided by an express finding regarding whether compliance concerns regarding patients with swallowing difficulties would provide a motivation to combine." *Id*. at 934-35.

II. DISCUSSION

The Federal Circuit has remanded to this Court to consider: (1) "the limited question of whether compliance concerns with patients who have trouble swallowing would provide a motivation to combine"; and (2) "its impact on the obviousness analysis." *Forest*, 918 F.3d at 938. After setting out the legal standard for obviousness, each issue is addressed turn.

A. The Legal Standard for Obviousness

A patent is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art [a 'POSA']." 35 U.S.C. § 103(a). Obviousness is a question of law based on the following underlying factual findings: (1) "the scope and content of the prior art"; (2) "the differences between the claimed invention and the prior art"; (3) "the level of ordinary skill in the art at the time of invention"; and (4) "any relevant secondary considerations, such as commercial success, long-felt but unresolved need, failure of others, copying, and unexpected results." *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 662–63 (Fed. Cir. 2000).

B. Whether Compliance Concerns Would Provide A Motivation to Combine

Defendants contend that the '476 patent is invalid for obviousness based on a motivation to combine prior art references that disclose the compound asenapine with other prior art references that disclose sublingual and buccal dosage forms of other drugs. The burden falls on Defendants to show by clear and convincing evidence that: (i) "a skilled artisan would have been motivated to combine the teaching of the prior art references to achieve the claimed invention," and (ii) "the

skilled artisan would have had a reasonable expectation of success in doing so." *Procter & Gamble Co. v. Teva Pharma. USA, Inc*., 566 F.3d 989, 994 (Fed Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc*., 480 F.3d 1348, 1361 (Fed. Cir. 2007)).

1. A reason or motivation to combine

Two of Defendants' prior art references—Chien and Gancher—are articles discussing the advantages of sublingual and buccal administration routes. D.I. 474 at 19 (citing D.I. 475-2, Ex. 18 at 47-50 (Chien), Ex. 19 at 2-4 (Gancher)). But neither the Chien nor Gancher references suggest that one of those advantages is improved patient compliance or overcoming swallowing difficulties. In addition, neither reference discusses using sublingual or buccal formulations for antipsychotics, such as asenapine. Accordingly, the Chien and Gancher references provide no motivation to develop sublingual or buccal formulations of any drug to address patient compliance concerns. And they provide no motivation to develop sublingual or buccal formulations of asenapine for any reason.

Three of Defendants' prior art references—U.S. Patent No. 4,371,516 (the "'516 patent"), U.K. Patent No. 2,111,423 (the "'423 patent"), and Motwani—disclose that sublingual and buccal routes of administration can be used as an alternative to orally administered tablets for patients that may be uncooperative or have difficulty swallowing. *See* D.I. 475-1, Ex. 2 at 1:9-24 ('516 patent); *Id*., Ex. 4 at 1:1-5, 50-63 ('423 patent); D.I. 475-2, Ex. 16 at 1 of 12 (Motwani). But none of these references discuss schizophrenic or bipolar patients as the type of patient experiencing compliance problems or difficulty swallowing. Instead, one of the references discusses geriatric and pediatric patients "in particular" as the type of patients that raises compliance concerns. *See* D.I. 475-1, Ex. 2 at 1:9-24 ('516 patent). In addition, none of the references identify asenapine in particular or antipsychotics in general as suitable for a sublingual or buccal route of administration.

See D.I. 475-1, Ex. 2 at 3:24-43 ('516 patent) (identifying several "[t]ypical drugs" and disorders that can be administered by means of the invention, but not antipsychotics); *Id*., Ex. 4 ('423 patent) (failing to describe any disorders or drugs suitable for a sublingual or buccal dosage form); D.I. 475-2, Ex. 16 at 1 of 12 (Motwani) (identifying the fourteen drugs "currently" given by sublingual and buccal routes of administration, which treated disorders related to the cardiovascular, respiratory, or central nervous systems).

At most, these three references—the '516 patent, '423 patent, and Motwani—demonstrate that individual elements of claims 1 and 4 of the '476 patent separately existed in the prior art, i.e., the compound asenapine and sublingual dosage forms of other drugs were known at the relevant time. But "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 418-19 (2007). "There must be some suggestion or motivation to combine the references." *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd*., 821 F.3d 1359, 1368 (Fed. Cir. 2016).

In addition, a general understanding that a certain dosage form may improve patient compliance is not enough, by itself, to show that a POSA would have been motivated to develop a specific drug or a drug for a specific illness using that dosage form. *See AstraZeneca Pharm. LP v. Anchen Pharm., Inc*., 2012 WL 1065458, at *99-100 (D.N.J. Mar. 28, 2012) (finding that "no specific motivation existed … to create a sustained-release formulation of quetiapine based on the general notion that sustained release treatments improved patient compliance as compared to [immediate release] drug formulations"); *cf. Bayer Pharma AG v. Watson Labs., Inc*., 874 F.3d 1316, 1322 (Fed. Cir. 2017) (finding that an oral disintegrating tablet ("ODT") to treat erectile

dysfunction ("ED") was obvious where "[a]ll six of the prior art references … identify ED drugs as ODT formulations").

Indeed, the '516 and '423 patents were issued in 1983. But, by the 1994 filing date of the '476 patent, approximately 11 years later, there were only "about five or six drugs that were actually given sublingually and were on the market sublingually compared to all the rest of the drugs in the world." D.I. 314 at 958:15-20. And none of those sublingual drugs were antipsychotics. D.I. 312 at 412:24-413:11. Thus, Defendants' prior art references disclosing a general compliance advantage did not motivate either the widespread development of sublingual and buccal dosage forms or the particular development of a sublingual and buccal form of asenapine.

2. Reasonable Expectation of Success

Even if a skilled artisan was motivated in 1994 to solve compliance problems for schizophrenic or bipolar patients using orally administered tablets, there was no reasonable expectation that sublingual and buccal routes of administration would lead to success.

The testimony in the record from clinical experts establishes that sublingual and buccal dosage forms are more difficult to use for patients with schizophrenia and bipolar disorders. D.I. 315 at 1032:9-1035:24. Plaintiff's clinical expert, Dr. McIntryre, testified that sublingual formulations require an atypical set of instructions that must be carefully followed, including refraining from food and water for a certain period of time and holding the dosage form in the mouth under the tongue for a period of time. D.I. 315 at 1032:9-1033:16, 1034:1-1035:24, 1094:7-1096:12. "Defendants' own expert clinician, Dr. Hollander, agreed that sublingual administration would not improve patient compliance." *Forest*, 257 F. Supp. 3d. at 688 (citing D.I. 301 at 705:15-

706:4).[2] This testimony contradicted the testimony of Defendants' non-clinical expert, Dr. Jacobs. *Forest*, 257 F. Supp. 3d. at 688 n. 22. But Judge Robinson nevertheless found, based on the testimony of the clinical experts, that "sublingual dosage forms are more burdensome to schizophrenic patients." *Id.* at 688.

In addition, Defendants' own prior art references do not provide a reasonable expectation of success. Instead, some references, like the Motwani, cast doubt. Motwani notes the increased interest in sublingual and buccal routes of administration, but also acknowledge the "limitations" to their use. D.I. 475-2, Ex. 16 at 1. For example: "The tablet must be kept in place and not chewed or swallowed for the period, sometimes prolonged, over which absorption is occurring." *Id*. Other references, like Schmauss, provide no insights. The Schmauss reference documents a clinical trial in which the opioid buprenorphine, used to treat pain, was sublingually administered to ten schizophrenic patients in order to determine the antipsychotic effects of opioids. D.I. 475-1, Ex. 5 at 1. But it did not document the burdens involved in the sublingual administration of buprenorphine or whether or not patients experienced compliance problems. And it involved a different type of drug and a small number of patients. Thus, Schmauss has limited utility. D.I. 315 at 1042:3-25. For the foregoing reasons, I find that there was neither a motivation based on compliance concerns to combine the drug compound asenapine with sublingual and buccal dosage forms nor a reasonable expectation of success.

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[2] Defendants argue that Dr. Hollander testimony about compliance was directed only to Saphris and not the state of the art as of 1994. D.I. 474 at 23. Judge Robinson, however, relied on this testimony to determine whether there was a motivation to combine based on bioavailability concerns. *Forest*, 257 F. Supp. 3d. at 688. Thus, Judge Robinson, who oversaw the bench trial, understood the testimony to be directed to the state of the art in 1994, and I will not second guess her understanding of the testimony.

C. The Impact of the Motivation to Combine Findings on the Overall Obviousness Analysis

I must now consider the impact of my findings on compliance concerns to the overall obviousness analysis. Judge Robinson found that several factors weighed in favor of non-obviousness, and those findings were affirmed on appeal.

First, Judge Robinson found that the oral or IV administration of asenapine could cause severe cardiotoxic side effects, and the sublingual formulation of asenapine provided a solution to this unrecognized problem in the art. *Forest*, 257 F. Supp. 3d at 687. As the Federal Circuit explained, "where a problem was not known in the art, the solution to that problem may not be obvious, because 'ordinary artisans would not have thought to try at all because they would not have recognized the problem.'" *Forest*, 918 F.3d at 935 (quoting *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013)).

Second, Judge Robinson found that sublingually administered asenapine met the long-felt but unmet need for a safe, effective, and tolerable atypical antipsychotic useful to treat schizophrenia and mania. *Id*. at 690. The Federal Circuit found no error in Judge Robinson's analysis of long-felt need, although it did note that this was not "particularly strong" evidence of nonobviousness. *Id*. at 936-37.

The Federal Circuit did find error in Judge Robinson's analysis of unexpected results. *Forest*, 918 F.3d at 937. The Federal Circuit explained that a POSA could not have been surprised that the sublingual administration of asenapine successfully resolved the serious cardiotoxic event when they were unaware the problem even existed.

Viewing these previous findings together with my own findings on the lack of a motivation to combine, I conclude that Defendants have not established by clear and convincing evidence,

that the '476 patent was obvious. Therefore, my compliance concerns findings does not disturb Judge Robinson's ultimate holding that the '476 patent is valid.

III. CONCLUSION

In response to the Federal Circuit's instructions on remand, I find that compliance concerns with patients who have trouble swallowing would not have provided a motivation to combine. In addition, my conclusions on the motivation to combine does not disturb Judge Robinson's previous ruling that the '476 is not obvious. An appropriate order will be entered.